Bone changes in alcoholics: a review

E González-Reimers*, F Santolaria-Fernández, J Alvisa-Negrín

Abstract

Introduction

Alcoholism may damage the skeleton. In addition to a direct effect of ethanol, many other mechanisms are involved which should be considered in the clinical evaluation of alcoholic patients. We will review the mechanism and clinical consequences of bone alterations observed in alcoholics.

Conclusion

Osteoporosis is the main metabolic disease observed in alcoholic patients. The main factors involved in its pathogenesis are: a direct effect of ethanol, associated malnutrition, liver disease, altered hormone profile and cytokine pattern, and alcoholic myopathy. Osteoporosis may lead to bone fracture. It improves with ethanol withdrawal.

Introduction

Alcohol is a toxic compound which affects virtually any organ, leading to many diseases of variable severity. One of these organs is the skeleton. Alcoholism is associated with impaired growth, osteoporosis and bone fracture, sometimes also with osteomalacia, and infrequently with aseptic necrosis, mainly of the femoral head. In addition, there is a delay in fracture healing and surgical treatment is associated with increased morbidity among these patients. Mechanisms are partially known and include direct effects of ethanol on bone synthesis and also systemic alcoholism-associated alterations, such as impaired nutrition, malabsorption, liver disease, altered hormonal profile, altered cytokine pattern, and, possibly, myopathy, neuropathy and factors related to the peculiar lifestyle of the alcoholic patient (Table 1). Osteopenia, which is frequently observed among alcoholics, contrasts with the finding of several researchers who report that consumption of low to moderate amounts of ethanol (in population-based epidemiological studies) may be associated with increased bone mineral density (BMD) and a relative reduction in the risk of fracture, including hip fracture. However, even in these studies, risk that relates the amount of ethanol consumed and the presence of osteopenia and/or fracture adopts a J-shaped curve.

In this review, we will focus on the mechanisms underlying metabolic bone disease and bone fracture in (heavy) alcoholic patients. Aseptic osteonecrosis is an uncommon condition not related to metabolic bone disease. In a study on 77 cases, ethanol was present in 33 cases. Pathogenesis is unknown.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki, 1964, and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

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Table 1 Main factors involved in ethanol-associated bone alterations.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Main mechanism(s) involved</th>
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</thead>
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<tr>
<td>Direct effect of ethanol</td>
<td>Toxic effect on osteoblast function (oxidative damage?)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Decreased absorption of calcium and vitamin D nutrients, in general</td>
</tr>
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<td></td>
<td>Altered hormonal profile (altered IGF-1, vitamin D, gonadal hormones)</td>
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<tr>
<td>Chronic pancreatitis</td>
<td>Altered nutrient absorption. Malnutrition</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Decreased osteoid synthesis. Decreased IGF-1 levels. Altered nutrient intake</td>
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<tr>
<td>Alcoholic hypogonadism</td>
<td>Altered trophic effect on bone and muscle</td>
</tr>
<tr>
<td>Alcoholic myopathy/neuropathy</td>
<td>Altered trophic effect on bone (probably via Wnt beta catenin pathway)</td>
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<tr>
<td>Alcohol-mediated iron excess</td>
<td>Altered osteoblast function</td>
</tr>
<tr>
<td>Zinc deficiency (malnutrition; alcohol?)</td>
<td>Altered bone growth</td>
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<tr>
<td>Pro-inflammatory cytokines</td>
<td>Possibly, increased bone resorption</td>
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<tr>
<td>Life style</td>
<td>Trauma. Bone fractures. Decreased nutrient intake</td>
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Altered bone synthesis: direct effects of ethanol

In 1965, Saville described that bone weight of young alcoholics was similar to that of post-climacteric non-alcoholic persons. Indeed, alcoholics frequently show decreased bone mass. Fractures are common, especially rib fractures, often bilateral or multiple. In a classic study performed more than 30 years ago, Israel et al. found that rib (or vertebral) fractures were present in 57 out of 198 patients, versus only 4 out of 218 controls. Lindsell et al. in 1982, reported that chest fractures (most rib fractures) in patients with liver disease suggested an alcoholic aetiology with 95% specificity and 28% sensitivity, so they might be useful in the detection of alcoholism. Other studies have confirmed these results. In a previous study, we found that rib fractures were present in 40 out of 81 alcoholics, especially among those with ruptured familial or social links. In that study, BMD did not differ among patients with or without fractures, although it was lower among the alcoholic group than in the age and sex-matched controls. The relative importance of underlying metabolic disease and bone fracture in alcoholics was also challenged by Wilkinson et al., who found trauma, but not bone metabolic disease, as a major cause of fracture among these patients. However, later, it was clearly shown that ethanol exerts a direct effect on bone, especially on bone synthesis, thus decreasing it. Several studies report decreased serum levels of osteocalcin – a biochemical marker of bone synthesis – among alcoholics. In a study on 124 patients and 38 controls, marked differences in osteocalcin levels were observed, together with reduced BMD at different sites of the body. These results are similar to previously reported data (Figures 1a and 1b). These observations, showing a direct toxic effect of ethanol and, especially, acetaldehyde on osteoblastogenesis, are in accordance with the experimental findings of Giuliani et al. In addition, ethanol-mediated increased production of reactive oxygen species (ROS) may be involved in reduced osteoblast activity although, in a series of 54 cases, we did not find any relation between osteocalcin and malondialdehyde, a lipid peroxidation product. Interestingly, both osteopenia and decreased bone mass are reversible alterations since prolonged abstinence increases bone mass13, and in non-cirrhotic alcoholics, markers of bone synthesis arise after seven days of abstinence. In a study on 60 patients subjected to densitometric analysis, both at admission to our hospital unit and six months later, those who stopped drinking showed an increase in total BMD in contrast with those who did not.

In close relation with the inhibition of bone synthesis, there are data which support an inhibitory effect of ethanol on bone growth. In two
function impairment, but in a recent study on 72 cirrhotics, 37 of them alcoholics, it was found there was a high prevalence of osteopenia, which was not related to liver dysfunction, but to reduced physical activity, low lean body mass and reduced sunlight exposure. Those patients with the highest estradiol levels showed the highest BMD values\textsuperscript{18}. In a study on 52 cirrhotics and 72 non-cirrhotics, the former showed, in general, lower BMD values, but using a multivariate approach, the parameter which showed closest association with low BMD was the amount of ethanol consumed\textsuperscript{19}. Calcium levels are low in cirrhotic alcoholics, even corrected by albumin, and this is also usually accompanied by a decrease in vitamin D levels. Despite the altered vitamin D metabolism, osteomalacia rarely ensues. In fact, osteomalacia was not observed in any of the 52 heavy alcoholics with histologically confirmed liver cirrhosis, who were subjected to bone biopsy\textsuperscript{20}.

**Protein–calorie malnutrition**

Protein–calorie malnutrition is a major feature of many alcoholics\textsuperscript{4}. In various clinical and experimental studies using multivariate analysis, it was shown that malnutrition was the main factor involved in decreased bone mass\textsuperscript{14,18}. If amino acids are not available, synthesis of osteoid is impaired. In addition, malnutrition strongly affects the metabolism of IGF-1. IGF-1 acts on bone promoting osteoblast activity and bone synthesis. Indeed, a close relation between IGF-1 and osteoid amount ($r_{ho} = 0.38; p < 0.0001$) was observed among rats treated with the Lieber de Carli model\textsuperscript{16}, fully in accordance with the trophic effect of IGF-1 on osteoblasts and the almost universal finding of a relationship between BMD and IGF-1 in alcoholics. Alternatively, protein–calorie malnutrition is related to marginalisation and isolation of the alcoholic patient, who progressively loses his

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### Figure 1: Serum osteocalcin levels in patients and controls:

Osteocalcin was clearly, significantly reduced among alcoholics (Figure 1a; $t = 5.30; p < 0.001$), who also showed lower total body bone mineral density, especially marked at pelvis (Figure 1b; $t = 5; p < 0.001$). In a subset of these patients, serum telopeptide was also increased (Figure 1c; $Z = 4; p < 0.001$), suggesting the presence of increased resorption, a finding not shared by all the authors.
familial and social links and adopts bizarre eating habits. IGF-1 also plays an outstanding role as a growth factor. In addition to the effects on bone growth, IGF-1 increases muscle mass and strength. In a study performed by our group involving 101 patients, a direct correlation was observed between handgrip and IGF-1 levels ($r = 0.29; p = 0.003$; unpublished data). Increased muscle mass and strength are related to increased bone synthesis.

**Altered hormone levels: muscle atrophy**

Cortisol leads to bone resorption, but the extent of alteration this hormone may bring about in osteopenia in alcoholics is unclear. Usually, cortisol levels are not elevated or are only marginally elevated despite physical signs of hypercortisolism (i.e., so-called ‘Pseudo Cushing’ of the alcoholics). Most alcoholic patients with Pseudo Cushing syndrome are obese – obesity counteracting the possible direct effect of cortisol on bone breakdown, although, in contrast, cortisol promotes muscle atrophy. In several clinical and experimental studies, we have failed to find a relation between cortisol and BMD, or differences in cortisol levels between alcoholics and non-alcoholics.

Besides its action on calcium metabolism and bone mineralization, vitamin D also exerts an important effect on the muscle. A receptor for vitamin D has been isolated in muscle fibres, and we recently reported a relationship between vitamin D deficiency and type II muscle fibre area. This result is in accordance with the well-described proximal weakness in patients with osteomalacia and vitamin D deficiency, and establishes a link between muscle atrophy and vitamin D deficiency in alcoholics. Therefore, vitamin D deficiency would negatively affect the bone with two synergistically-acting detrimental effects on bone mass.

Alcohol exerts a double effect on hypothalamic-hypophyseal-gonadal axis, leading to hypogonadism and decreased testosterone levels. Testosterone has an anabolic effect on the bone, and shares with vitamin D and IGF-1 a trophic effect on the muscle. Therefore, testosterone deficiency leads to muscle atrophy. In addition, ethanol exerts a deleterious effect on the muscle, mainly decreasing muscle protein synthesis. Both acute and chronic myopathy have been described in the alcoholic patient. Chronic myopathy, characterized by muscle atrophy (especially type II fibres) and weakness, could also play a role on bone loss. Muscle mass and strength are major determinants of bone mass, and both are affected in alcoholics with myopathy and altered hormonal profile.

The bone is sensible to the load exerted by muscle contraction, by activation of the Wnt/β-catenin pathway. This leads to increased bone formation and osteoblast proliferation, and to decreased bone resorption. Sclerostin antagonizes Wnt/β-catenin signalling by binding to low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and LRP6), thereby inhibiting osteoblast function, differentiation and survival. Therefore, high sclerostin levels should be associated with decreased bone mass and bone turnover, but this is not always the case. Only some preliminary results are available for sclerostin among alcoholics, showing an inverse correlation with osteocalcin, but a direct one with telopeptide suggesting a role in bone breakdown.

**Trace elements**

Some trace elements could be involved in bone changes of the alcoholic patient. It was shown that iron may hamper bone development and it is well-known that iron increases in alcoholics. Although iron excess may cause osteopenia altering osteoblast function, one experimental study shows no relation between bone mass and bone iron in alcohol-treated rats.

Zinc is involved in bone synthesis. Some studies have shown that zinc supplementation leads to bone growth in zinc-deficient growing animals or in premature children. Zinc deficiency has been described in alcoholics. The addition of zinc increases reduced BMD in alcoholic rats, but the clinical significance of this finding is uncertain. It has been also hypothesized that certain trace elements may be beneficial due to their antioxidant activity (e.g., selenium), but no consistent results are available. The same is valid for the use of several substances with antioxidative properties, which theoretically could counteract the ROS-mediated inhibition of osteoblast function.

**Increased breakdown: cytokines and the OPG/RANK-L system**

In contrast with the inhibition of osteoblast function, the effects of ethanol on bone resorption are less clear. Some authors have reported increased breakdown in alcoholic cirrhosis – although not in Child A cirrhotics, whereas in other studies bone resorption was not significantly altered or even reduced. Serum parathyroid hormone (PTH) levels are frequently normal despite serum calcium levels being in the lower limit of the normal range or even decreased. However, in disagreement with the presence of a low turnover osteoporosis, but in accordance with some other studies, we found increased serum telopeptide levels among 90 alcoholics, including non-cirrhotic ones, compared with controls ($Z = 4.00; p < 0.001$; Figure 1c), suggesting increased bone resorption. Bone resorption depends on differentiation and activation of osteoclasts, a process which involves binding of receptor activator of nuclear factor kappa B (RANK) ligand (RANK-L) to RANK, expressed in pre-osteoclasts cell mem-

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Alcoholics. Osteoprotegerin (OPG) is a soluble decoy receptor which ultimately impedes binding of RANK-L to RANK, therefore preventing bone resorption. Several cytokines, including tumour necrosis factor (TNF-α), Interleukin (IL)-1 and IL-6, activate RANK-L, whereas bone metabolically-active hormones, such as oestrogens, vitamin D, corticosteroids and parathyroid hormone modulate osteoprotegerin32. In the absence of OPG, RANK-L becomes activated by TNF-α and bone resorption ensues. Moreover; activation of the Wnt-beta catenin system blocks osteodensitogenesis by increasing the OPG/RANKL ratio33. In alcoholics, TNF-α, IL-1 and IL-6 are raised, as a consequence of activation of Kupffer cells by gut-derived gram negative bacteria, which reach the portal system due to ethanol-mediated increased intestinal permeability34. In addition, alcoholics frequently suffer infectious and inflammatory processes, such as pancreatitis or pneumonia, each of which is accompanied by secretion of pro-inflammatory cytokines. The role of pro-inflammatory cytokines on bone changes in the alcoholics constitutes, therefore, a real possibility; future research in this field is necessary to better characterize alcoholic and hepatic osteodystrophy. In a previous study, we found raised values of OPG among alcoholics, especially among cirrhotics35, a result comparable to that found by other authors in cirrhotics and in other diseases characterized by osteopenia, in which raised OPG has been interpreted as expression of a compensatory mechanism.

Conclusion

Osteoporosis is the most-frequently observed skeletal complication of alcoholism, and affects both cirrhotics and non-cirrhotics, although, in general, it is more severe in patients with liver function impairment. Bone synthesis is especially depressed, but some controversy exists regarding bone resorption. A direct effect of ethanol, liver disease, protein–calorie malnutrition, altered hormone and, possibly, zinc and iron levels, and muscle atrophy related to alcoholic myopathy and/or neuropathy seem to be involved in its pathogenesis. Possibly, pro-inflammatory cytokines, raised in alcoholics, may activate osteoclasts via the OPG/RANK-L system and contribute to decreased bone mass.

Abbreviations list

BMD, bone mineral density; IGF-1, insulin-like growth factor 1; IL, interleukin; OPG, osteoprotegerin; PTH, parathyroid hormone; R, reactive oxygen species; TNF, tumour necrosis factor.

References